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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/[illegible]092	12/30/97	JOLLEY	P 1155.005

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NORMAN J CRUSE
CHIRON CORP
INTELLECTUAL PROPERTY R440
P O BOX 8097
EMERYVILLE CA 94662-8097

EXAMINER
SCHWARTZMAN,R

ART UNIT	PAPER NUMBER
1636	11

DATE MAILED: 10/12/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/001,039	Jolly et al.
Examiner	**Group Art Unit**
Robert Schwartzman	1636

X Responsive to communication(s) filed on *Aug 3, 1999* .

This action is **FINAL.**

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

X Claim(s) *1-11, 37-58, and 61-68* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

X Claim(s) *37-56* is/are allowed.

X Claim(s) *1-11, 57, 58, and 61-68* is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

X The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____ .

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

This Office action is in response to the Response to Restriction Requirement filed August 3, 1999. Claims 12-36, 59, 60 and 69-90 have been canceled. Claims 1-11, 37-58 and 61-68 are pending in this application.

Election/Restriction

Applicant's election without traverse of Group I, claims 1-11, 37-58 and 61-68 in Paper No. 10 is acknowledged. The non-elected claims were canceled in Paper No. 10.

Information Disclosure Statement

It is noted that the Information Disclosure Statement (IDS) filed February 11, 1998 has been misplaced by the Office and that the copies of the references cited in the IDS filed March 19, 1998 have also been misplaced. It is requested that applicants file a replacement IDS for the one originally filed February 11, 1998 and file copies of the references cited in both IDS's.

Specification

The specification contains amino acid and nucleic acid sequences (page 160, line 22; Figures 1, 3, 6, 7) that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2) but are not present in the Sequence Listing and/or identified by the appropriate sequence identifier numbers. Applicant must provide a corrected paper copy and computer readable copy of the Sequence Listing and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). A full response to this Office action must include a complete response to the requirement for a new Sequence Listing.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-11, 58 and 61-68 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The present claims are broad, encompassing any replication defective recombinant retrovirus having the claimed properties and any therapeutic protein (claims 61-63).

The nature of the invention is a retroviral vector capable of long term systemic expression of a therapeutic protein following intravenous administration.

An analysis of the prior art as of the effective filing date of the present application shows that, although there have been a large number of studies regarding expression of a therapeutic protein *in vivo* using a retroviral vector, there are still major obstacles to long term expression of a protein at significant levels, particularly in a human.

The relative skill of those in the art of vectors and gene expression is high.

The area of the invention is unpredictable. As state above, there have been innumerable studies on retroviral gene expression in mammals. However, it has been exceedingly difficult to achieve long term expression of a gene at significant levels, either in small or large mammals (Verma *et al.*, page 240; Anderson, pages 25-26). Obstacles include transcriptional shut-off of the gene, loss of cells comprising the retroviral vector and choice of appropriate regulatory sequences. Additionally, promising results obtained in small mammals (mice, rats) are frequently not seen in large mammals, including humans (Verma *et al.*, page 240, column 3). Thus, there is not a strong correlation between small animal results and results in humans.

The present specification provides insufficient direction or guidance to support the claimed invention. The specification discusses many possible techniques for the preparation and administration of retroviral vectors. However, no indication is made as to what particular methods lead to long term systemic expression of a therapeutic protein following intravenous administration or how to identify the methods and techniques necessary for long term expression. No correlation is made between the disclosed animal model results and the ability for the same results to be obtained in humans.

Several working examples are disclosed in which a retroviral vector encoding a therapeutic protein (factor VIII (FVIII) or growth hormone (GH)) is administered intravenously to an animal and expression of the protein detected. In Example 18 rabbits were injected with a retrovirus encoding FVIII. No expression was detected until 56 days after the administration, after which some of the animals exhibited long term expression. In Example 19 rabbits were injected with a retrovirus encoding GH. Expression was detected on and off (days 7, 20-36, after day 56) but not in a stretch of 30 consecutive days. In Example 20 three week old mice were injected with a retrovirus encoding GH. Expression was detected after a lag of 14-48 days, after which some animals exhibited long term expression. In Example 21 adult mice were injected with a retrovirus encoding GH. Expression was detected on day 3 only. In Example 24 juvenile dogs was injected with a retrovirus encoding FVIII. One dog expressed the protein long term following a lag of 13 days. In Example 26 hemophilic dogs were injected with a retrovirus encoding FVIII. Expression was detected at days 4-10 and perhaps after day 35. In none of these examples was the protein expressed for the 30 days immediately following the administration of the retrovirus as there was a lag period of a few days to a few weeks in each example. Therefore, the claims as written are not supported by the examples. Additionally, only 3 out of the 6 examples showed expression of the protein at any time for at least 30 consecutive days, and only in a small percentage of the injected animals. No examples of expression in humans are disclosed.

The quantity of experimentation necessary to carry out the claimed invention is high as the skilled artisan could not rely on the prior art or the present specification to teach how to make and use a retrovirus which will induce long term expression of a therapeutic protein in a human following intravenous administration. The specification discloses some animal models of retroviral expression but none of them exhibit the claimed expression pattern. No correlation can be made between the animal results and possible human results as there is insufficient predictability based on the animal models. The prior art acknowledges the difficulties in using retroviral vectors to achieve long term expression of a protein in a human. The skilled artisan would therefore have to practice trial and error experimentation to determine how to achieve long term expression of a therapeutic protein using a retrovirus.

Based on the broad scope of the claims, the nature of the invention, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to make a retrovirus preparation capable of inducing long term expression of a therapeutic protein when administered intravenously to a human.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11, 57, 58 and 61-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 57 are vague and indefinite as the phrase "capable of infecting" does not adequately define when and under what conditions the capability exists, *i.e.*, it implies that there are times at which the retrovirus can infect human cells and times at which it cannot. It is suggested that the claims be amended to recite "said recombinant retrovirus infects human cells".

Claims 6, 58 and 61 are vague and indefinite as the phrase "capable of inducing long term expression" does not adequately define when and under what conditions the capability exists, *i.e.*, it implies that there are times at which the retrovirus can induce long term expression and times at which it cannot. It is suggested that the claims be amended to recite "induces long term expression".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mulligan *et al.* in view of either Mason *et al.* or Takeuchi *et al.*

Mulligan *et al.* teaches a retrovirus (MFG) encoding FVIII (column 26, line 27-column 27, line 38). The MFG vector is deleted for gag, pol and env and therefore is replication defective

(column 11, lines 29-43). Retroviral particles were prepared using an amphotropic packaging cell line, thus producing retroviruses capable of infecting human cells (column 27, lines 39-44). The B domain deletion of FVIII is a deletion of amino acids 743-1648. This leaves a single B domain SQN tripeptide at amino acids 1649-1651, therefore meeting the definition of an SQN deletion in the present specification (page 26, lines 8-12). Mulligan *et al.* does not teach retroviruses that are resistant to degradation by human complement. Mason *et al.* teaches retroviruses that are resistant to degradation by human complement due to expression from the retrovirus of a chimeric complement inhibitor protein (column 13, lines 33-48). Takeuchi *et al.* teaches (entire document) retroviruses that are resistant to degradation by human complement due to the fact that they are produced from a human packaging cell line. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make a retroviral vector encoding FVIII as taught by Mulligan *et al.* and to modify the retroviral vector to be resistant to degradation by human complement by the method of Mason *et al.* or Takeuchi *et al.*, motivated by the teaching of Mulligan *et al.* that the retroviral FVIII vector was intended for administration for humans and the teachings of Mason *et al.* and Takeuchi *et al.* that the complement-resistant retrovirus would be more efficient for *in vivo* gene delivery applications.

Claim 57 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kay *et al.* in view of either Mason *et al.* or Takeuchi *et al.*

Kay *et al.* teaches (page 118, column 1) a replication defective retrovirus (LNCX) encoding factor IX (FIX). Retroviral particles were prepared using an amphotropic packaging cell line, thus producing retroviruses capable of infecting human cells. Kay *et al.* does not teach retroviruses that are resistant to degradation by human complement. Mason *et al.* teaches retroviruses that are resistant to degradation by human complement due to expression from the retrovirus of a chimeric complement inhibitor protein (column 13, lines 33-48). Takeuchi *et al.* teaches (entire document) retroviruses that are resistant to degradation by human complement due to the fact that they are produced from a human packaging cell line. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make a retroviral vector encoding FIX as taught by Kay *et al.* and to modify the retroviral vector to be resistant to degradation by human complement by the method of Mason *et al.* or Takeuchi *et al.*, motivated by the teaching of Kay *et al.* that the retroviral FIX vector was intended for administration for humans and that greater efficiency of gene delivery was needed (page 119, column 1) and the teachings of Mason *et al.* and Takeuchi *et al.* that the complement-resistant retrovirus would be more efficient for *in vivo* gene delivery applications.

Conclusion

Claims 1-11, 57, 58 and 61-68 are rejected. Claims 37-56 are allowable. Claims 5-11, 37-56, 58 and 61-68 are free of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Schwartzman whose telephone number is (703) 308-7307. The examiner can normally be reached on Monday through Friday from 6:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached at (703) 308-4003. The fax number for this group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703)-308-0196.

October 7, 1999

ROBERT A. SCHWARTZMAN
PATENT EXAMINER